randomly formed therein, the micro particles having a combination of average particle size and average particle surface roughness which cooperate in an autogenous manner to essentially prevent loss of the micro particles from an injection site;

a4 (cont.)

selecting a compatible physiological vehicle that will promote injection of the micro particles but once injected need not retain injected micro particles in situ.

REMARKS:

In accordance with the above amendments, claims 1-3, 16, 17 and 23 have been amended and new claims 26-30 added. Claims 1-30 remain in the case, and no claim has been allowed.

It is noted that various ones of the slate of claims originally presented have been rejected under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 based on one or more cited references. These rejections will next be addressed.

First, claims 1, 2, 16 and 25 stand rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Politano and the applicants' specification. The Politano reference concerns the injection of Polytef paste to cure urinary incontinence. The composition of Polytef paste for injection is described on page 182, column 1, at the beginning of the "Discussion" section of the Politano et al reference. The system is an injectable paste consisting of poly(tetrafluoroethylene) particles measuring 50 to 100 microns in glycerine and polysorbate. As described in the

article, the implant "achieves firm consistency and retains its shape and position at the injection site". It is further noted that the Politano et al reference carries a 1974 copyright date.

With regard to Politano et al, applicants would like to direct the Examiner's attention to another reference cited by the applicants in the present application. That reference is Malizia, Jr., et al, "Migration and Granulomatous Reaction after Periurethral Injection of Polytef (Teflon)", JAMA, June 22-29, 1984, Vol. 251, No. 24. This article is dated some ten years after Politano et al and takes issue with the degree of success achieved by Polytef, especially with regard to migration of the particles and ensuing granulomatous reactions in various parts of the bodies of injected patients. Without intent to disparage Polytef, this is clear documentary evidence based on clinical investigation which reveals serious drawbacks and side effects likely to occur in following the method of Politano et al. It is further clear that there is nothing disclosed in either of the cited Politano et al articles that would lead one to believe that such undesirable particle migration would occur. The problem itself is nowhere recognized; it follows that clearly no solution to any problem with regard to migration of the polytetrafluoroethylene beads is suggested.

The method of the present invention requires the use of particles as the implant material which do not migrate and further do not require external retention means to prevent them from

migrating prior to their encapsulation by the growth of new tissue. This further requirement with regard to the micro implants of the present invention clearly represents an inventive step which, for example, with respect to Polytef, represents the difference between success and possible serious ensuing side complications. While such differences may at first appear subtle, in reality they are extremely important to the long-term success of the implant.

Therefore, it is believed the rejection of claims 1, 2, 16 and 23 based on Politano et al and applicants' specification has clearly been met and should not stand. The present particles are believed to clearly distinguish over those disclosed by Politano et al. Applicants do not nor do they need to argue that they are the first ever to inject particles into the disclosed areas of interest. The next rejection concerns claims 3-6, 8-15, 17-21 and 24, which have been rejected under 35 U.S.C. § 103 as being unpatentable over the politano et al publications as applied in the first enumerated rejection and further in view of Wallace et al (U.S. Patent 4 803 075) and Berg et al (U.S. Patent 4 837 285). Applicants respectfully traverse this rejection also for reasons of record above with respect to Politano et al and for reasons enumerated next below with regard to Berg et al, Wallace et al and any combination of the references.

Berg et al is directed to collagen-based compositions for augmenting soft tissue, wound dressings, implants, injectable formulations or other drug delivery systems. While the Berg et al

reference seems quite relevant at first, especially as it may have to do with the augmenting of soft tissue, it is soon apparent that his micro implant material is quite different from that of the present invention. The Berg et al material is required to be resorbable collagen matrix beads. The implant beads of Berg et al are implanted for the purpose of stimulating wound closure or other natural tissue growth in the vicinity of the implant but not the permanent encapsulation or retention of the implanted matrix beads themselves. These are specifically designed to be resorbed and replaced. For example, note with regard to the wound dressing and injectable solution uses of the collagen matrix beads by Berg et al that with regard to wound dressing, in Examples 8 and 9, the collagen beads "will resorb within 14 days" (see column 8, line 32 and line 49). Further, with regard to Example 10 at column 8, lines 62 and 63, according to Berg et al, "the collagen matrix beads are remodelled and replaced by native collagen within 36 days". In any event, it is clear that the collagen matrix beads of Berg et al are not intended to remain in situ with respect to tissue augmentation or other uses of them.

The Wallace et al reference deals with improving the intrusion or intrudability of injected beads by the use of aqueous suspensions including a biocompatible fluid lubricant. That reference is concerned with the physical problems associated with injecting the material itself and promoting the spreading of the particles of the material outward through and along the adjacent

tissue. It is clear that particles of biomaterial in the range 1 to 30 microns disclosed by Wallace et al will not remain in situ once implanted or if made of collagen will be resorbed. It is further quite apparent that the Wallace et al reference is directed to improving dispersion, not retention in situ. The same (at least with regard to resorption) is true of the collagen fibrils disclosed by Wallace et al. Thus, while Wallace et al talks about soft tissue augmentation, it is clear that their injected material is not permanent and any inventive step is directed to increasing the tissue penetration and ease of injection of micro particles and is clearly not concerned with problems associated with long-term retention of the injected material in situ.

With regard to the three combined references, then, it is clear that none disclose or are concerned with the problems of maintaining injected micro particles at the site of soft tissue augmentation. It is clear that the references taken either singularly or in combination do not even reveal the existence of the problems addressed and solved by use of micro implants in the manner of the present invention. There is clearly no motivation based on a consideration of the cited references to, as the Examiner suggests, use porous particles in the treatment of urinary incontinence to prevent particle migration from the implant site simply because nothing in the prior art references teaches that any advantage would be gained by doing so. Silence concerning the existence of the problem at all certainly does not give rise to any

solution or any reason to apply a solution other than piecing things together through hindsight. Furthermore, as noted, it is not the porosity of the particles per se which provides prevention of migration.

Applicants believe that the rejections based on a combination of Politano et al, Berg et al and Wallace et al have been fully met and that the present invention represents a new and unique approach to alleviating gastric reflux and urinary incontinence which represents a definite inventive step that improves long-term treatment.

It is further believed that, in view of the above, the specific page references with respect to Politano et al and Wallace et al with respect to claims 4-6 which may reveal certain materials and characteristics, do not teach anything particularly relevant to the inventive steps of the present invention.

Further with the respect to the additional citation of Patent 4 828 827 to Henderson et al with respect to claims 7, 22 and 25, it is submitted that applicants do not pretend to be the first to suggest the use of polyvinyl pyrrolidone (PVP) itself in conjunction with soft tissue augmentation. This is not to say that Henderson et al recognize other than that a crosslinked PVP hydrogel can be used as the implant to augment soft tissue. They do not use it as a vehicle for other implant materials.

Perhaps an analogy should be drawn here to the alleged inert hydrogel of crosslinked PVP itself being a suitable soft tissue

augmentation substance. It may be legitimately compared to silicone gel which is also a well-known inert biocompatible material, because of the similar softness of the gels. Silicone gel can be fragmented by mechanical trauma such as the action of muscles, bones, tendons, movement of the skin, etc. The fragmentation of such silicone gel even when crosslinked for maximum cohesive ability, has resulted in the distant migration of this inert gel along tissue planes. Not only does this destroy its effectiveness as a soft tissue augmentation method (i.e., the augmentation moves elsewhere leaving a valley where once was a mountain) but, this distant migration can also cause mechanical problems.

Assuming the PVP crosslinked gel is inert as Henderson et al claim and assuming it lasts for a very long time and is not phagocytized or otherwise degraded by the body's environment, the mechanical presence of this material in the region of a nerve, for example, can cause mechanical pressure on that nerve which will cause the nerve to malfunction. In fact, it may cause the nerve to wither and die. This is a well-known and previously described phenomenon wherein silicone gel was liberated from an implant site by muscular motion, dissected along the fascial planes of the pectoralis muscle to its insertion near the brachial plexus, down the brachial artery to the brachial plexus such that the gel was recovered in distal nerve sites as far distal as the median nerve where it was responsible for median nerve compression (neuropathy).

This phenomenon was found to be irreversible and the inert gel, of course, irretrievable.

Therefore, Henderson et al's studies using bb size amounts of crosslinked PVP gel implanted in the chest beneath the skin show the crosslinked, high molecular weight material is not readily dispersed by the body when placed in a non-weight bearing, unstressful area. Similar studies were used for years to support the use of silicone gel and silicone oil for micro-droplet injection for the treatment of wrinkles and small dents in the face. Although there were numerous glowing testimonial reports of how this material functions, long-term studies showed that even with the most carefully placed micro-droplets of inert gel, migration of the particles was the common finding, not the exception; and this migration of relatively inert silicone gel was found to mechanically block lymphatics. In several cases reported by Jurkiewicz et al of Emory University and others, even after seven years of what appeared to be a good correction of a facial indentation, massive inflammation subsequently occurred with severe tissue destruction. This was thought to be due to the inert gel clogging the lymphatic system so the normal defense mechanisms could not function well. In this way, a trivial infection, for instance, from a hair follicle or sweat gland became an overwhelming abscess with substantial tissue destruction.

As a result of these findings, silicone gel and oil were not approved for this use by the FDA. This comparison shows that there

are possible drawbacks and the virtues alleged by Henderson et al: (1) inertness, (2) gel-like softness, tell only part of the story. They are the exact virtues shared by silicone gel and/or fluid that has been so vigorously rejected by the regulatory agencies and many plastic surgeons. The Henderson et al material clearly is not the same as nor is it used for the same purpose as that in the present invention.

The PVP vehicle of the present invention itself is deliberately of a chemical structure and molecular weight so as to be generally resorbed and passed from the body through the renal system intact and within a fairly short period of time. It is clear that the present use of PVP, in particular, is as a vehicle which will not linger or even maintain the particles in situ to prevent migration. It is believed that the claims properly distinguish over the cited prior art.

The Examiner's concerns with the prior art statement filed on July 9, 1992 have been noted. Accordingly, a Supplemental Information Disclosure Statement dated October 8, 1992 has been submitted in the present application containing a listing of all patents and foreign documents on Form PTO-1449 so that all the references will be considered. Applicants regret any noncompliance with PTO rules in their earlier submission.

In accordance with the above amendments taken together with the remarks submitted herewith, applicants believe the present claims to be patentably distinct over the prior art known to them

cited either singularly or in combination. A reexamination and allowance of the claims is earnestly solicited.

Respectfully submitted,

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